FDA's Approach to Meeting the Challenge of Pandemic Influenza Preparedness

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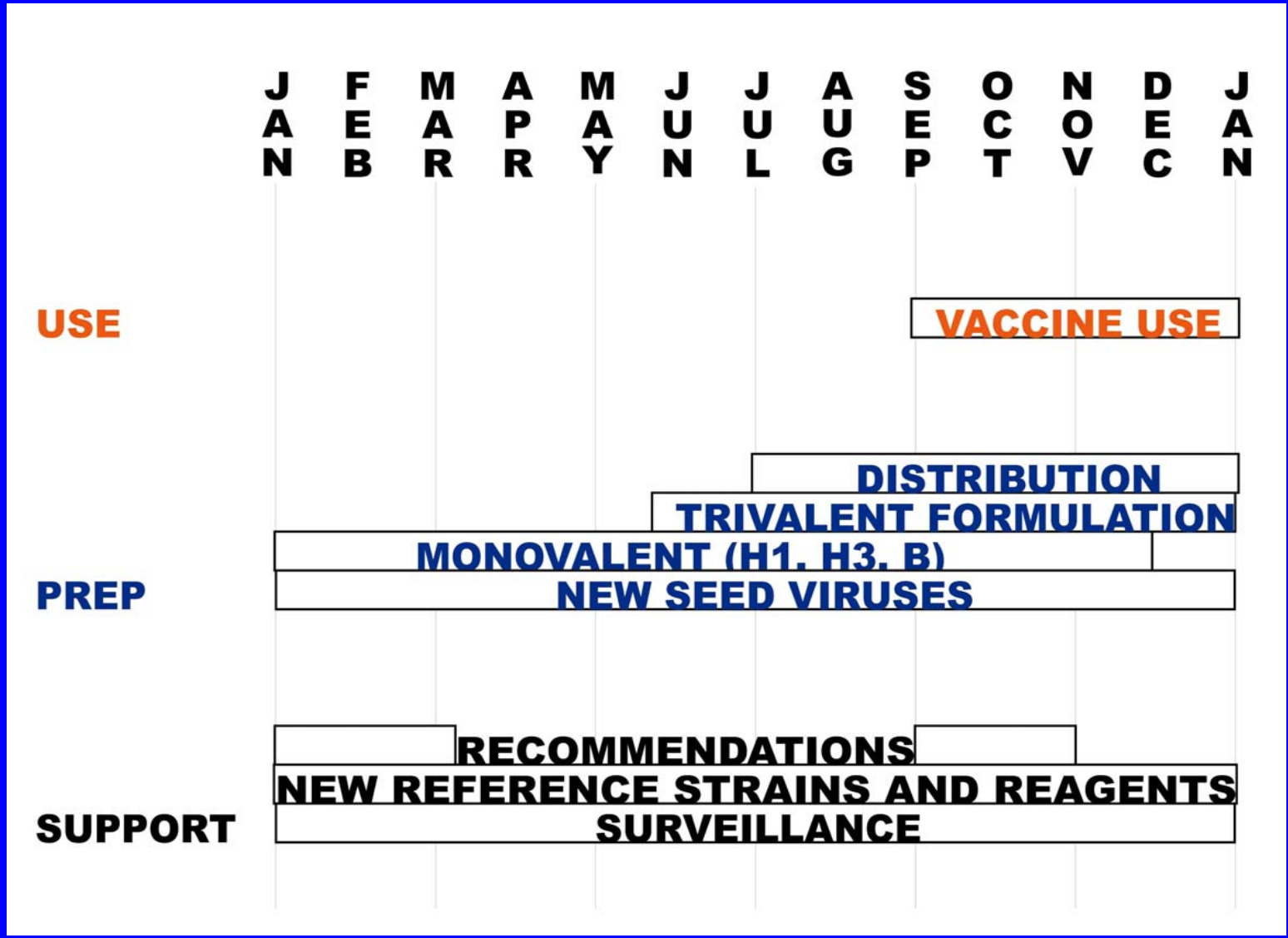
Meeting the Pandemic Vaccine Challenge: Overview and Actions

- ✓ Increasing manufacturing diversity and capacity
- ✓ **Developing** needed pathways and regulatory processes to speed vaccine availability
- ✓ Facilitating vaccine manufacturing and availability
  - – scientific and related technical needs
  - – enabling both current and evolving technologies:

Meeting the Pandemic Vaccine Challenge: Overview and Actions

- ✓ Assuring safety and public confidence
- ✓ Considering pathways to prevent a pandemic
- ✓ Thinking and working globally

Timelines for Vaccine Production



Increasing Manufacturing Diversity and Capacity

- Markets (demand and sales) are main driver
- In last 2-3 years, increasing vaccine stimulating interest of global manufacturers in US market
- 2004 shortage further accelerated interest
- FDA and industry interactions helpful:
  - Intensive interactions to assure potential access to vaccine under IND for 2004-5 season: data reviews and facility inspections made 5 mill doses avail, if needed
  - Several manufacturers have expressed interest in US licensure and FDA is interacting proactively with them
  - CBER utilizing accelerated approval mechanism

Lessons Learned Lead to Other FDA Steps to Strengthen Supply

- **Globalization:**
  - **Information sharing agreements and relationships both completed and being developed**
    - **Pre and post-licensure**
  - **Encouraging global vaccine development plans and regulatory cooperation/harmonization**
- **Annual inspections of flu manufacturers**
- **GMP initiative**
  - **Increased communications and enhanced preventive approaches including on vaccine GMPs**

Pathways to Speed Availability: Annual US Influenza Vaccine

- **Each year, any of the previous three vaccine strains may be replaced with a new strain**
- **Strain changes based on evaluation of circulating wild-type strains**
- **Submission of a prior approval manufacturing supplement to an existing license is required for strain changes**
- ***FDA does not require clinical data for approval of these annual supplements for licensed manufacturers of inactivated flu vaccine***

Basis for Use of Accelerated Approval Authorities

- 21 CFR 601.40
  - Meaningful therapeutic benefit
    - Serious or life-threatening conditions
    - Lack of available alternative therapies
  - Influenza vaccine shortage applicable
  - CDC population of benefit ~ 185 million doses
  - For pandemic strains, unmet medical need per se
- 21 CFR 601.41
  - Surrogate endpoints
    - Reasonably likely to predict clinical benefit
    - Clinical endpoint studies to confirm

Pathways to Speed Availability: Accelerated Approval for Inactivated Flu Vaccines

- FDA considers there to be a short supply
- CBER will consider HI anti-HA antibody levels as a likely surrogate marker for efficacy
- Therefore, accelerated approval can be sought based on immunogenicity provided:
  - validated assays
  - post-approval studies of clinical efficacy
  - complete manufacturing data, controls & inspections
  - satisfactory safety data; clinical trials and data from experience with same vaccine under foreign licensure can contribute

Pathways to Speed Availability: Accelerated Approval for Inactivated Flu Vaccines II.

- GSK and ID Biomedical have each indicated that they will seek licensure under this accelerated approval mechanism (others may in future) – shortening time to potential approval by 1-2 years
  - GSK Fluarix approved in August 2005
- Immunogenicity data can also be useful:
  - to bridge efficacy data to additional populations and to evaluate manufacturing changes
  - to determine HA dose and number of doses needed for a novel strain (e.g. For pandemic strains)

Pathways to Speed Availability: Licensure of Pandemic Vaccines

- **FDA views a pandemic strain used in a licensed manufacturing process as a strain change**
  - **Biologically, a new HA antigen is just that, another HA antigen, such as used in routine strain changes**
  - **For licensed manufacturers using licensed processes, would not be treated as a *new vaccine* but as a supplement with *some clinical data important***

Pathways to Speed Availability: Licensure of Pandemic Vaccines

- **Either a wild type or a reassortant virus (including virus derived by reverse genetics) can be used**
  - **FDA has no problems with use of recombinant or cell culture based technologies in strain production so long as adequate controls and characterization**

Pathways to Speed Availability: Licensure of Pandemic Vaccine (II)

- Generate potential pandemic vaccines manufactured according to a licensed process
- Conduct clinical studies using these pandemic vaccine during interpandemic period
  - NIAID studies (e.g. of H5N1) will provide critical information on dose and schedule
  - Future generalizability of such data to other strains unclear: immunogenicity of various pandemic strains may differ
- Prepare qualified seed strains and high growth reassortants representing major known and evolving pandemic antigens

Pathways to Speed Availability: Licensure of Pandemic Vaccine (III)

- Studies of strain cross-protection in HA types, methods to predict based on sequence analysis
- Advance preparation of needed reagents for manufacturing: e.g. antigens & antisera
- Evaluation of existing assays and consideration of development of new technological approaches (e.g. to potency, Abs, sterility) that may speed manufacturing and regulatory review

Thinking Ahead: Enabling New Approaches and Technologies (Overview)

- Even with aggressive and successful efforts to diversify and strengthen US inter-pandemic production, capacity may still be inadequate for true widespread pandemic in US, and, almost certainly, for global needs
- Antigen sparing and other new technologies should be evaluated before a pandemic

Enabling New Technology – Antigen Sparing Strategies

- **Addition of adjuvant to vaccine formulation.**
  - **Results (published and unpublished) in past have been conflicting: adequate studies are needed before adopting**
  - **Would be considered a new product (requiring BLA)**

Enabling New Technology – Antigen Sparing Strategies

- Safety and efficacy (immunogenicity) data required
  - Simplest - aluminum (extensive experience in licensed vaccines)
  - Early studies should demonstrate rationale (e.g., *significant* increases in immunogenicity with acceptable safety profile) and determine dose
  - Novel adjuvants or those with previous safety signals would require more safety data
  - Supporting manufacturing and product information also needed
- If proof-of-concept and other studies favorable, Phase 3 studies should be pursued in interpandemic period

Other Antigen Sparing Strategies

- Changing route of vaccine delivery
  - Simplest change might be i.d. using needle and syringe but raises practicality issues
  - Safety and efficacy (immunogenicity) data needed
  - Other delivery methods promising: need data
- Use of immune stimulators, (e.g. use of patch with heat-labile toxin).
  - Safety and efficacy data required
  - Such strategies are in relatively early development; lack of experience will require safety testing

Enabling New Technologies: Cell Culture & Recombinant Vaccines

- There are significant potential advantages in flexibility afforded by non-egg based technologies
  - Despite problems, egg based manufacturing has been successful & cost effective and, to date, other technologies have not been marketed or widely used
  - FDA has licensed other cell culture derived and recombinant based vaccines and has no special regulatory concerns with these technologies for flu
    - We encourage their development and provide intensive interactions with sponsors

Enabling New Technologies: Cell Culture & Recombinant Vaccines

- **Scientific/technical challenges include:**
  - **Cell based: usual safety issues (i.e. tumorigenicity, adventitious agents), sufficient yield, manufacturing scale & cost**
  - **Recombinant: Antigenicity and protective immune response**

Other New Technologies

- Cross-protective antigens
- Live attenuated vaccines
  - Provide multiple immunogens, some may be cross-protective
  - May enhance more rapid development of immunity
  - May raise potential containment issues for public health and agriculture

Assuring Safety and Public Confidence

- Clear communication: full transparency and continuing discussions re: risks/uncertainties of pandemic vs. vaccine safety/effectiveness
- Where time permits, obtain additional safety database on several thousand individuals pre-licensure
- Facilitate AE reporting & surveillance through VAERs & other databases

Considering Potential Future Pathways to Preparedness?

- For a pandemic to be a pandemic a prerequisite is the lack of population immunity
- Can we conceptualize pandemic preparedness in a routine prevention rather than crisis mode?
- Should we consider earlier building of immunity against evolving virulent pandemic threat strains?

Considering Potential Future Pathways to Preparedness?

- Should we consider the potential for integration of such preparedness into more routine influenza immunization, as we do for emerging epidemic strains?
- Transparency, public dialogue, a non-crisis environment, and acceptance/demand would be important for any such approaches to be considered

Thinking globally and acting both locally and globally

- Work with public health and industry partners to facilitate building global vaccine capacity – benefits all
- Regulatory and other cooperation to facilitate potential sharing and transnational use of vaccines
  - Payoffs in both pandemic and interpandemic settings

Thinking Globally and Acting Both Locally and Globally

- Potential to vaccinate at geographic site(s) of evolving virulent pandemic strain transmission threat, even prior to widespread human to human spread
  - May slow or halt pandemic – modeling may be helpful
  - May allow better understanding and additional modeling of unique scientific and non-scientific challenges in early intervention against pandemic threat strains

Summary

- When the pandemic arrives, there won't be time to develop new manufacturing processes and the ability to increase the existing capacity will be limited
- The primary source of vaccine will come from using the pandemic strain to manufacture inactivated vaccine according to current licensed processes

Summary

- **FDA is working with partners to diversify and strengthen influenza vaccine manufacturing, and providing flexible rapid regulatory pathways – *progress has been made***
- **FDA views pandemic vaccines made using licensed processes as supplements rather than new licenses – *this can speed & reduce the burden and costs of pandemic response***

Summary

- Either wild-type virus or high growth reassortants (made by traditional methods or reverse genetics) can be used to manufacture vaccine
- Initiation of clinical trials to provide data that supports the use of 15 µg of HA or some other amount for potential pandemic strains and informs the number of doses needed will help prepare for the real pandemic
- Further advance preparation and improvement of strains, reagents, assays and standards would be beneficial

Summary

- Scientific needs in manufacturing and in evaluating safety and effectiveness of antigen sparing approaches, and of new vaccines as well as of non-egg based technologies is best addressed before a pandemic – key studies are beginning
- Pathways exist to allow consideration of benefits and risks of early intervention against virulent potential pandemic strains, including potential integration into public health preparedness, as we do for annual influenza strains
- Epidemiological studies to evaluate the impact of the pandemic vaccines on disease burden would be of great importance, as would surveillance for vaccine-associated adverse events